DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202811

WRITTEN REQUEST

Forest Laboratories, LLC
Attention: Linda Kunka, M.A.
Associate Director, Regulatory Affairs
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Ms. Kunka:

Reference is made to your August 3, 2015 Proposed Pediatric Study Request for Linzess™ (linaclotide).

BACKGROUND:

Functional gastrointestinal disorders affect approximately 25 million people in the United States and have a significant economic impact due not only to direct medical costs, but also to lost wages and decreased productivity. The prevalence and natural history of functional gastrointestinal disorders in children is not as well understood, and well defined diagnostic criteria have been lacking. The prevalence of irritable bowel syndrome in children and adolescents is not well described and disparate figures have been reported. Community-based studies have reported rates as low as 0.2% for children under 12 years of age; however, rates of up to 14% have been reported for older school-age children in some studies. The prevalence of chronic constipation among pediatric patients in the Western world is estimated at 3%.

Irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC)[1] in children are chronic diseases, often overlapping with each other and other functional GI disorders. Both can have a significant impact on quality of life in pediatric patients, and many children diagnosed with IBS and/or CIC continue to experience signs and symptoms into adulthood. There are currently no approved therapies for IBS-C or CIC in pediatric patients. Stool softeners, dietary fiber supplementation, antispasmodics, and antidepressants are among the treatments used in the management of pediatric IBS-C and CIC; however an approved treatment for these indications is needed.

Linaclotide is a guanylate cyclase-C (GC-C) agonist approved August 30, 2012, for the treatment of adults with irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation

[1] The term chronic idiopathic constipation (CIC) is being used in this document to remain consistent with the adult indication for CIC; however, the terms CIC and functional constipation may be used interchangeably in clinical practice to refer to constipation that is characterized by a chronic time course and for which there are no anatomical, structural, or biochemical abnormalities.

(CIC). Both linaclotide and its active metabolite bind to GC-C and act locally on the luminal surface of the intestinal epithelium. Activation of GC-C results in an increase in both intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP). Elevation in intracellular cGMP stimulates secretion of chloride and bicarbonate into the intestinal lumen, mainly through activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel, resulting in increased intestinal fluid and accelerated transit.

The primary safety concern identified during the linaclotide clinical development program resulted from a finding of lethality in neonatal/juvenile mice receiving linaclotide in a dose-ranging study. This resulted in a boxed warning to avoid use in pediatric patients until further animal studies were completed. Since that time, the Applicant has determined that the mechanism of death in young juvenile mice was due to dehydration caused by a fluid shift into the intestine due to stimulation of the expression of the target receptor (GC-C). These data along with data from a review of the literature regarding GC-C ontogeny suggest an age-dependency of the pharmacodynamic response and indicate that linaclotide would not be safe to administer to children under the age of 2, including neonates.

To obtain needed pediatric information on linaclotide dosing, safety, and efficacy, as well as develop an appropriate Patient Reported Outcome (PRO) measure in pediatric IBS-C patients and understand the potential impact of linaclotide on chloride transport in certain Cystic Fibrosis (CF) genotypes, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

Under current regulations [21 CFR 201.57(f)(9)(iv) in the 2008 CFR], a new claim in a pediatric population could be established by extrapolating the effectiveness results of adequate and well controlled studies in adults for the same entity as long as the pathophysiology of the disease, and the effect of the drug are sufficiently similar between adults and pediatric patients.

For drugs such as linaclotide which act locally in the gut, modelling exposure-response reliably is difficult or impossible; therefore full extrapolation of linaclotide's efficacy from affected adults with chronic idiopathic constipation or irritable bowel syndrome-constipation subtype to affected pediatric patients is not possible.

The multiple adequate and well controlled studies described subsequently in this document are intended to determine linaclotide's effectiveness and safety for the treatment of chronic idiopathic constipation and irritable bowel syndrome-constipation subtype in the pediatric ages described.

- *Nonclinical study(ies)*:

  It is recognized that linaclotide exerts pharmacodynamic effects through the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein. However, there is currently insufficient information to assess the potential benefit of the active moiety in other non-CIC/IBS indications, such as manifestations of intestinal obstruction and constipation in patients with cystic fibrosis. In order to understand better the potential impact of linaclotide on chloride transport in certain CF genotypes, conduct the following nonclinical study(ies):

Assess the impact of linaclotide on chloride transport in a subset of Cystic Fibrosis (CF) genotypes expressed in nonclinical models. Provide positive or negative evidence to determine the effect of linaclotide on the activation of the CFTR chloride channel (e.g., via an animal Cystic Fibrosis (CF) model or cell culture/line) across varying mutant CF genotypes.

- *Clinical studies:*

For each study in this written request, the protocols and any subsequent amendments must be submitted for review and agreement with the Agency prior to trial initiation.

A. Required supportive studies to support the pediatric development of linaclotide in pediatric patients with IBS-C and CIC:

   a. A clinical research study to characterize guanylate cyclase-C mRNA expression in duodenal and colonic mucosal biopsies in children ages 0 to 17 years.

- *Objective: To quantitate guanylate cyclase-C (GC-C) mRNA expression levels in duodenal and colonic mucosal biopsies in children ages 0 to 17 years (inclusive).*

- *Patients to be studied: This study will be conducted in children from birth to age 17 years (inclusive) who are undergoing a diagnostic upper or lower GI tract endoscopy or both as part of their medical care.*

- *Number of patients to be studied: Biopsy samples will be obtained from 60 children having upper GI tract endoscopies and 60 children having lower GI tract colonoscopies; stratified by age group (birth to <24 months, ≥24 months to < 6 years, 6 years to < 12 years, 12 years to < 18 years), with 15 subjects per age group for upper and lower GI tract endoscopies/colonoscopies, respectively.*

- *Study endpoints/statistical information: The statistical analysis will employ regression analysis to assess the relationship between the GC-C mRNA levels and age.*

   b. Patient Reported Outcome Measure Development: Determine via concept elicitation/cognitive debriefing interviews or focus groups if abdominal pain and bowel movement frequency are the most important sign and symptom in pediatric patients with IBS-C and ensure that the instructions and language used in the items and response options are clear and well-understood by the children and caregivers. Assess the validity of reports of abdominal pain (e.g., consider a pictorial scale) and bowel movement frequency in children (ages 7-17 years). Your PRO should be sufficiently developed to be used in your phase 3 IBS-C clinical trial.

   c. Observer-reported Outcome Measure Development: Develop an observer-reported outcome (ObsRO) measure to assess bowel movement frequency for use with caregivers of younger children (e.g., 7-10 years, depending on the results of the

qualitative interviews) who may not be able to reliably report for themselves. Your ObsRO should be sufficiently developed to be used in your phase 3 IBS-C clinical trial.

B. Required clinical studies of linaclotide in CIC and IBS-C indications:

a. Study 01: Randomized, double-blind, placebo-controlled, parallel group, dose-ranging study for the treatment of **chronic idiopathic constipation** in children ages 6-17 years.

- *Objectives: To assess the safety, tolerability, and efficacy of linaclotide administered orally to children aged 6 years to 17 years with chronic idiopathic constipation prior to the initiation of the corresponding confirmatory Study 03. To allow choice of an optimal single dose of linaclotide to evaluate in Study 03 and to guide selection of the dose range for studies in children with chronic idiopathic constipation 2 to <6 years of age, if needed.*

- *Patients to be studied: 6 years to 17 years of age; stratified by age group (6-11 years and 12-17 years) with a minimum of 40% of patients within each age group.*

- *Number of patients to be studied: Approximately 160 total to receive placebo, a low dose, medium dose, high dose, or the approved adult dose of linaclotide (only patients 12 to 17years may be randomized to the approved adult dose).*

- *Study Endpoints:*

  The standards for measurement for the specified endpoints must be submitted for review and agreement with the Agency prior to study initiation.

  Pharmacokinetic Endpoints: Characterization of PK parameters for linaclotide and its active metabolite (MM-419447) will include sparse PK sampling.

  Primary Efficacy Endpoint: Change from baseline in 4-week overall spontaneous bowel movement (SBM) frequency rate (SBMs/week) during the Treatment Period.

  Secondary Efficacy Endpoints should include the following BM characteristics and abdominal symptoms as recorded by either a patient or interviewer-administered version of the PRO diary:

    - *Abdominal pain*
    - *Incomplete evacuation after each BM*
    - *Stool consistency (modified Bristol Stool Form Scale [mBSFS]) of each BM*

- *Statistical information: Study 01 is a dose-ranging study intended to provide descriptive statistics only.*

b. Study 02: Randomized, double-blind, placebo-controlled, parallel group, dose-ranging study for the treatment of **irritable bowel syndrome with constipation** in children ages 7 – 17 years.

- *Objectives: To assess the safety, tolerability, and efficacy of linaclotide administered orally to children aged 7 years to 17 years with IBS-C prior to initiation of the corresponding confirmatory Study 04. To allow choice of an optimal single dose of linaclotide and an optimal primary outcome measure to evaluate in Study 04..*

- *Patients to be studied: 7 years to 17 years of age; stratified by age group (7 – 11 years and 12 – 17 years) with a minimum of 40% of patients within each age group.*

- *Number of patients to be studied: Approximately260 total randomized to placebo, a low dose, medium dose, high dose or the approved adult dose of linaclotide (only patients 12 to 17 years may be randomized to the approved adult dose).*

- *Study Endpoints:*

  The standards for measurement for the specified endpoints must be agreed upon with the Agency prior to trial initiation.

  Pharmacokinetic Endpoints: Characterization of PK parameters for linaclotide and its active metabolite (MM-419447) will include sparse PK sampling.

  Primary Efficacy Endpoint: Change from baseline in 4-week overall SBM frequency rate (SBMs/week) during the Treatment Period.

  Secondary Efficacy Endpoints should include the following BM characteristics and abdominal symptoms as recorded by either a patient or interviewer-administered version of the PRO diary:

    - *Abdominal pain*
    - *Incomplete evacuation after each BM*
    - *Stool consistency (modified Bristol Stool Form Scale [mBSFS]) of each BM*

- *Statistical information: Study 02 is a dose-ranging study intended to provide descriptive statistics only.*

c. Study 03: Randomized, double-blind, placebo-controlled, parallel group confirmatory study for the treatment of **chronic idiopathic constipation** in children ages 6-17 years.

- *Objectives: To assess the safety, tolerability, and efficacy of linaclotide administered orally to children aged 6 years to 17 years with chronic idiopathic constipation. To provide evidence supporting response to treatment and disease course of chronic idiopathic constipation in older pediatric patients (6-17 years) to inform whether extrapolation to younger pediatric patients (2-5 years) is appropriate.*

- *Patients to be studied: 6 years to 17 years of age; stratified by age group (6-11 years and 12-17 years) with a minimum of 40% of patients within each age group.*

- *Number of patients to be studied: 120 total (60/arm), stratified by age group with a minimum of 40% of patients within each age group. Sample size may be increased based on the results of Study 01.*

- *Study Endpoints:*

  The standards for measurement for the specified endpoints must be submitted for review and agreement with the Agency prior to trial initiation.

  Pharmacokinetic Endpoints: These will be determined based on the PK results from Study 01.

  Primary Efficacy Endpoint: The primary efficacy endpoint will be a responder endpoint based on improvements in bowel movement frequency over a 12-week period; the responder threshold will be derived from data from Study 01. The responder definition must be agreed upon with the Agency prior to trial initiation.

  Secondary Efficacy Endpoints should include the following BM characteristics and abdominal symptoms as recorded by either a patient or interviewer-administered version of the PRO diary:

    - *Abdominal pain*
    - *Incomplete evacuation after each BM*
    - *Stool consistency (modified Bristol Stool Form Scale [mBSFS]) of each BM*

- *Statistical information:*

  - *The sample size must be adequately powered (e.g., 85%) to detect the study drug's clinical benefit. This will be based on the acceptable clinical meaningful effect size which will be determined from the pediatric data collected in Study 01.*

  - *For the primary endpoint, i.e., responders at the end of study duration, the Cochran-Mantel-Haenszel test should be the primary analysis method.*

  - *The intent-to-treat population should be defined in the same way as your safety population, i.e., all randomized patients who receive at least one dose of double-blind investigational drug product.*

  - *The final protocol and statistical analysis plan (SAP) must be submitted and agreed upon with the Agency prior to conducting the trial. The SAP must include, but is not limited to, the primary and key secondary endpoints, primary analysis methods as well as the multiple comparison procedure for controlling the study-wise type I error rate, missing data imputation method, and rationale for sample size calculation.*

d. Study 04: Randomized, double-blind, placebo-controlled, parallel group confirmatory safety and efficacy study for the treatment of **irritable bowel syndrome with constipation** in children ages 7 – 17 years.

- *Objectives: To assess the safety, tolerability, and efficacy of linaclotide administered orally to children aged 7 years to 17 years with IBS-C.*

- *Patients to be studied: 7 years to 17 years of age; stratified by age group (7 – 11 years and 12 – 17 years) with a minimum of 40% of patients within each age group.*

- *Number of patients to be studied: 120 total (60/arm), stratified by age group with a minimum of 40% of patients within each age group. Sample size may be increased based on the results of Study 02.*

- *Study Endpoints:*

  The standards for measurement for the specified endpoints must be submitted for review and agreement with the Agency prior to trial initiation.

  Pharmacokinetic endpoints: These will be determined based on the PK results from Study 02.

  Primary Efficacy Endpoint: The primary efficacy endpoint will be a responder endpoint based on improvements in bowel movement frequency and abdominal pain over a 12-week period; the responder threshold will be derived from data from Study 02. The responder definition must be agreed upon with the Agency prior to trial initiation.

  Secondary Efficacy Endpoints should include the following BM characteristics and abdominal symptoms as recorded by either a patient or interviewer-administered version of the PRO diary:

    - *Abdominal pain*
    - *Incomplete evacuation after each BM*
    - *Stool consistency (modified Bristol Stool Form Scale [mBSFS]) of each BM*

- *Statistical information:*

  - *The sample size must be adequately powered (e.g., 85%) to detect the study drug's clinical benefit. This will be based on the acceptable clinical meaningful effect size which will be determined from the pediatric data collected in Study 02.*

  - *For the primary endpoint, i.e., responders at the end of study duration, the Cochran-Mantel-Haenszel test should be the primary analysis method.*

  - *The intent-to-treat population should be defined in the same way as your safety population, i.e., all randomized patients who receive at least one dose of double-blind investigational product.*

- *The final protocol and statistical analysis plan (SAP) must be submitted and agreed upon with the Agency prior to conducting the trial. The SAP must include, but is not limited to, the primary and key secondary endpoints, primary analysis methods as well as the multiple comparison procedure for controlling the study-wise type I error rate, missing data imputation method, and rationale for sample size calculation.*

e. Study 05: Open-label, long-term safety study enrolling children with **chronic idiopathic constipation or irritable bowel syndrome with constipation** who completed Studies 03 or 04.

- *Objective: To evaluate the long-term safety of oral linaclotide taken once daily by children, aged 6 years and older, with either CIC or IBS-C.*

- *Patients to be studied: 6 years to 17 years of age.*

- *Number of patients to be studied: At least 120 patients, the sample size to be determined based on the final sample size and on the number of patients who complete Studies 03 or 04.*

- *Study Endpoints: Study 05 is a long-term safety study. Safety endpoints are listed below.*

- *Statistical information: Safety will be assessed descriptively by summarizing adverse events, clinical laboratory values, vital signs, and ECG parameters. The sample size is not based on any statistical considerations and depends on the number of patients completing the lead-in confirmatory efficacy and safety studies.*

f. Study 06: Dose-ranging study for the treatment of **chronic idiopathic constipation** in children ages 2-5 years.

Note: Prior to initiation of Study 06, the nonclinical study, the clinical research study to characterize guanylate cyclase-C mRNA expression in duodenal and colonic mucosal biopsies in children aged 0 to 17 years, and the clinical studies in children ages 6 years to 17 years old in CIC (Study 01 and Study 03) must be completed and results reviewed by the Agency in order to better define the previously identified safety concern of fatalities observed in juvenile mice. The design of a dose-ranging study for the treatment of chronic idiopathic constipation in children aged 2-5 years will be determined based on the results of the aforementioned studies. The applicant will submit an amendment adding further details regarding the conduct of Study 06 or removing this study from this Written Request, pending the results of these aforementioned studies.

Studies 01 through 06:
The following sections apply to Studies 01 through 06, conducted in pediatric patients with CIC or IBS-C.

- *Representation of Ethnic and Racial Minorities:* The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial

minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- Measures of compliance must include eDiary compliance rate and unused study medication counts.

- *Safety Endpoints:*

  Safety outcomes must include:

  Physical examination, height, clinical laboratory tests (clinical chemistry, CBC, urine analysis), Electrocardiogram (ECG), Adverse event (AE) reports, vital signs, weight.

  The following adverse events must be actively monitored:

  Evidence of severe diarrhea, especially when accompanied by dehydration, volume depletion and/or significant electrolyte or ECG abnormalities.

  All adverse events must be monitored until symptom resolution or until the condition stabilizes.

  A Data Monitoring Committee (DMC) must be included. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees
  http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf

- *Known Drug Safety concerns and monitoring:*

  Linaclotide is contraindicated in children under 6 years of age. In neonatal mice, increased fluid secretion as a consequence of GC-C agonism resulted in mortality within the first 24 hours due to dehydration. Due to increased intestinal expression of GC-C, children under 6 years of age may be more likely than older children and adults to develop significant diarrhea and its potentially serious consequences. Linaclotide is also contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

  Diarrhea was the most common adverse event of linaclotide-treated patients in the pooled IBS-C and CIC double-blind placebo-controlled trials. Severe diarrhea was reported in 2% of linaclotide-treated patients. Evidence for severe diarrhea, especially when accompanied by dehydration, volume depletion and/or significant electrolyte or ECG abnormalities will be actively monitored throughout all clinical studies.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

    - *dosage form: oral capsule and oral solution*
    - *route of administration: oral*
    - *regimen: once daily, 30 minutes before the evening meal (dosing will depend on results of the dose ranging studies in CIC and IBS-C)*

Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that linaclotide is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more

frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

  Timeframe for submitting reports of the study(ies): Reports of the above studies must be submitted to the Agency on or before December 31, 2024. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to

conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call LCDR Cheronda Cherry-France, Regulatory Project Manager, at 301-796-7295.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIE G BEITZ
03/11/2016